REMARKS

The Office Action mailed November 4, 2008 has received and reviewed. In the Office Action, the Examiner has:

(1) objected to claim 24 as being of improper dependent form under 37 CFR 1.75(c);

(2) objected to claims 11 and 18 as being substantially duplicative of claim 8; and to claims 29 and 30 as being duplicative of claim 26;

(3) rejected claims 1, 2, 4-11, and 18-19 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement;

(4) rejected claims 20-31 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement;

(5) rejected claims 1-2, 8-11, and 18-19 under 35 U.S.C. § 102(b), as being anticipated by Aruffo et al. (U.S. Patent No. 5,540,926);

(6) rejected claims 1-2, 8-11, and 18-19 under 35 U.S.C. § 103(a), as being unpatentable over Aruffo et al. in view of Efstathiou et al. (U.S. Patent No. 6,193,980);

(7) rejected claims 1-2, 8-11, and 18-19 under 35 U.S.C. § 103(a), as being unpatentable over Aruffo et al. in view of Salvetti et al. (U.S. Patent No. 6,509,150);

(8) rejected claims 1-2, 8-11, and 18-19 under 35 U.S.C. § 103(a), as being unpatentable over Aruffo et al. in view of Baru et al. (U.S. Patent No. 6,207,456);

(9) rejected claims 1, 4-5, 8-11, and 18-19 under 35 U.S.C. § 102(b), as being anticipated by Bonyhadi et al.;

(10) rejected claims 1, 2, 4-5, 7-11, and 18-30 under 35 U.S.C. § 103(a), as being unpatentable over Zimmer et al. in view of Bonyhadi et al.

In connection with this response, claims 1, 7, 11, 18-20, 25, and 29-30 have been amended, and claims 12-17, and 24 have been cancelled. New claims 32-42 have been added. No new subject matter has been added in connection with the amendments. Upon entry of the

above amendments, claims 1-2, 4-11, 18-23, and 25-42 remain pending in the present application.

In view of the foregoing changes and the following remarks, Applicants respectfully request reconsideration of the claims.

Informalities

Claims 7 and 25 have been amended to correct typographical errors.

Objections

With respect to item (1) the Examiner has objected to claim 24 under 37 CFR 1.75(c) as being of improper dependent form. Without acceding to the propriety of the objection, Claim 24 has been canceled.

Indication of Potential Double Patenting

With respect to item (2), the Examiner has objected to claims 11 and 18 as being duplicative of claim 8, if claim 8 were to be allowed, and to claims 29 and 30 as duplicative of claim 26, if claim 26 were to be allowed. Without acceding to the propriety of the Examiner's comments, Applicants believe that the subject matter of claims 11, 18, 29, and 30 are distinguishable limitations. Claims 11 and 18 have been amended to clarify the feature of claim 8 that is being further limited, and claims 29 and 30 have been amended to clarify the feature of claim 26 that is being further limited.

Claim 11, as amended, further limits the CD8 α-chain as set forth in claim 8. In particular, the language in claim 11 further limits the CD8 α-chain to one that, when expressed by a target cell, inhibits an immune response against vector-associated antigens. Moreover, under MPEP 2173.05(g), functional language is acceptable to further define the invention. Likewise, claim 18, as amended, further limits the CD8 α-chain as set forth in claim 8. Specifically, the language in claim 18 further limits the CD8 α-chain to one that, when expressed, inhibits an immune response against the expression vector. Claim 29 and 30 have

also been amended in a similar manner to that set forth in claims 11 and 18, and further limit claim 26. In particular, claim 29 further limits the CD8 α-chain of claim 26 to one that, when expressed by a target cell, inhibits an immune response against vector-associated antigens. Similarly to claim 18, claim 30 further limits the CD8 α-chain of claim 26 to one that, when expressed, inhibits an immune response against the expression vector

Accordingly, Applicants submit that claims 11 and 18 are not duplicative of claim 8, and claims 29 and 30 are not duplicative of claim 26. Applicants respectfully request that the objection to these claims be withdrawn.

35 USC § 112

With respect to item (3), the Examiner has rejected claims 1, 2, 4-11, and 18-19 under 35 U.S.C. § 112, first paragraph for failing to comply with the written description requirement In particular, the Examiner has noted that there are a number of ways in which "separate expression" can be interpreted, and thus an artisan could not be able to determine that Applicant had possession of the claimed invention at the time of the invention. Applicants respectfully disagree.

Independent claims 1 and 19, as provided, recite, among other things, expression of a therapeutic molecule of interest and *separate* expression of a CD8 polypeptide by virtue of a second nucleic acid that encodes the CD8 polypeptide.

Support for *separate* expression of the first and second nucleic acid sequences, which will *a priori* produce *separate* polypeptide chains, can be found in paragraphs [014], [041], [106], and [108], of the present application as published.

Specifically, paragraph [014] discloses an expression vector comprising a nucleic acid sequence encoding for the CD8 polypeptide, and can include a nucleic acid sequence encoding a therapeutic transgene in the same vector as the CD8 polypeptide, or in another embodiment, in a separate vector. Paragraph [041] similarly describes an embodiment in which the CD8 molecule and therapeutic transgene are on one vector, and an alternative embodiment in which the CD8 molecule and therapeutic transgene are provided by separate expression vectors.

Paragraph [106], as published, provides that an expression vector, such as that of the present invention, includes transcriptional and translational regulatory nucleic acid sequences operably linked to a nucleic acid encoding a particular protein. In addition, each transcriptional and translational regulatory nucleic acid sequence, as provided in paragraph [108], includes transcriptional and translational start and stop sequences.

Since the present application provides that each transcriptional and translational regulatory nucleic acid sequence of the present invention is linked to the nucleic acid encoding of a particular protein, and since each transcriptional and translational regulatory nucleic acid sequence of the present invention includes start and stop sequences, it follows that whether the transcriptional and translational regulatory nucleic acid sequence encoding the protein that expresses the CD8 polypeptide and the transcriptional and translational regulatory nucleic acid sequence encoding the protein that express the therapeutic transgene are on the same vector or separate vectors, the presence of the start and stop sequences for each transcriptional and translational regulatory nucleic acid sequence can only result in the separate expression of the CD8 polypeptide and the therapeutic transgene.

Accordingly, Applicants submit that the subject matter of claims 1, 2, 4-11, and 18-19 is fully supported by the specification as originally filed. Applicants ask that this rejection be reconsidered and withdrawn.

With respect to item (4), the Examiner rejected claims 20-31 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement.

The Office Action at page 7 states:

> Claims 20-31 require that the CD8 alpha chain not be a fusion protein. The specification does not provide any disclosure that such was the contemplated invention, and in fact, actually discloses that it can be fusion, utilizing distinct transmembrane domains, as is further indicated in Claim 24. Moreover, no disclosure is given about any other form of fusion or absence thereof in the original disclosure and claims.

Applicants respectfully disagree. Paragraph [068] provides that "[i]n a preferred embodiment, the CD8 α-chain is not a fusion protein." It is well known in the art that a *fusion* protein is made when two different proteins are contiguously expressed as the same polypeptide

product of two genes fused in frame without an internal stop sequence (i.e., stop codon). Such a stop sequence is disclosed for the expression of the CD8 polypeptide and the therapeutic transgene of the present invention, as discussed above in item (3).

Accordingly, Applicants submit that the subject matter of claims 20-31 is fully supported by the specification as originally filed. Applicants ask that this rejection be reconsidered and withdrawn.

35 USC § 102(b)

With respect to item (5), the Examiner has rejected claims 1-2, 8-11, 18-19 as being anticipated by Aruffo et al., as further evidenced by WO 2004/042346 ("Wohlgemuth"), as demonstrated by U.S. Patent No. 5,851,806 to Kosvedi et al. ("Kosvedi" or '806).

Applicants respectfully submit that independent claims 1 and 19, as previously amended, provide for *separate* expression of CD8 extracellular domain and a therapeutic molecule of interest. Support for *separate* expression of the first and second nucleic acid sequences, which will *a priori* produce *separate* polypeptide chains, as discussed above in item (3), can be found in paragraphs [014], [041], [106], and [108], of the present application as published.

In contrast, nowhere does Aruffo et al. teach or disclose that CD8 should be separately expressed from GP39. Rather, Aruffo et al. states (1) that "in addition to gp39 amino acid sequence, the fusion proteins of the invention may further comprise a molecular tag" (col. 8, lines 11-12) and (2) that "suitable tag proteins include but are not limited to extracellular domains of type I membrane proteins such as CD8" (col. 8, lines 41-44). Clearly, Aruffo et al. stands for the creation of gp39 proteins, and as such, discloses a preferred fusion of gp39 and the extracellular domain of CD8. A *fusion* protein is made when two different proteins are contiguously expressed as the same polypeptide product of a single *fused* gene. Thus, *separate* expression of two polypeptides as the product of two genes is not the same as the expression of a *fusion* gene.

At page 10 of the present Office Action, it says that "Aruffo teaches placing the coding sequence of the GP39-CD8alpha into expression vectors which also comprise selection markers

under separate expression elements. Such selection marker coding sequences are nucleic acids of interest in selecting for the cells growing the vector and hence, the limitations of the claims are met." Applicants respectfully disagree.

Aruffo et al. do not expressly disclose selection markers in the paragraph bridging columns 6 and 7. Rather, the paragraph is a generic call to vector systems known in the art.

Moreover, even if Aruffo et al. had disclosed selection markers as part of the vector-host systems known in the art, the selection markers would not be *therapeutic molecules of interest*. Selection markers are for *selecting* cultures of cells that harbor a vector bearing the selectable gene, and are for ease of laboratory manipulations, but not for the purpose of treating genetic diseases. Therapeutic molecules, set forth in the claims at issue, on the other hand, are prophylactically or therapeutically beneficial to the cell or the tissue, organ, organ system, organism, or cell culture, for the purpose of treating genetic disease (see paragraph 052).

Since Aruffo et al. fail to teach or disclose *separate expression* of a CD8 polypeptide, and the use of a therapeutic molecule of interest, it can not be said that Aruffo et al. anticipate claims 1 and 19 of the present application. Furthermore, claims 2, 8, 9, 10, 11, and 18 are dependent from claim 1. Accordingly, claims 2, 8, 9, 10, 11, and 18 are also not anticipated by Aruffo et al.

It should be noted that the Examiner cited Wohlgemuth et al. solely to show that the CD8 sequence has been disclosed. Also, it should be noted that the Examiner cited Kovesdi et al. to show that the making of replication defective adenoviral vectors as plasmids includes the use of selection markers.

With respect to item (9), the Examiner has rejected claims 1, 4-5, 8-11, and 18-19 as being anticipated by Bonyhadi et al.

Independent claim 1 has been amended to recite *separate* transcription control elements *having associated* translational control elements for directing separate expression of said first and said second nucleic acid sequences.

Support for *separate* transcription control elements can be found in paragraph [108] of the present application as published. In particular, paragraph [108] states, "[i]n general, the transcriptional and translational regulatory sequences may include, but are not limited to,

promoter sequences, ribosomal binding sites, transcriptional start and stop sequences, translational start and stop sequences, and enhancer or activator sequences. In a preferred embodiment, the regulatory sequences include a promoter and transcriptional start and stop sequences." Control of transcription, as well understood in the art, includes controlling the start and stop of transcription. Moreover, as provided above, each transcriptional regulatory and translational regulatory sequences of the present invention is linked to the nucleic acid encoding a particular protein, and includes start and stop sequences, as provided in paragraph [106]. Since each nucleic acid sequence has its own transcriptional start and stop sequences, it follows that the transcription control elements are *separate*. It should be noted that when each of the first and second nucleic acid sequences has its own separate transcriptional start and stop sequences, the first and second nucleic acid sequences will be independently transcribed into separate mRNAs as a function of their separate transcription control elements, and ultimately translated into separate polypeptides.

Likewise, independent claim 19 has been amended to recite that the CD8 and therapeutic molecule of interest are separately expressed *as a function of separate transcription control elements*.

In contrast, Bonyhadi et al. fail to teach or disclose *separate* transcription control elements. Rather, Bonyhadi et al. teach a bicistronic mRNA message for expressing CD8 (used therein as cell-surface marker), and a *trans*-dominant mutant of the reverse transcriptase RevM10, which contains an internal ribosome entry site. As it says in Bonyhadi et al., in the legend of Figure 1 on p. 4708, "[t]ranscription is driven directly from the 5' long terminal repeat, yielding a single transcript." That is, Bonyhadi et al. teach a single mRNA transcript that yields two different proteins, by virtue of the internal ribosome entry site. That stands in contrast to the inventions of claims 1 and 19, namely, separate polypeptide chains of CD8 and a therapeutic molecule of interest, which result from translation of separate mRNA transcripts of CD8 and a separate therapeutic molecule of interest. The separate mRNA transcripts of CD8 and a separate therapeutic molecule of interest are a consequence of transcription controlled by *separate* transcription control elements.

Since Bonyhadi et al. fail to teach or disclose *separate transcription control elements*, Applicants submit that independent claims 1 and 19, as amended, are not anticipated by Bonyhadi et al. Claims 2, 4, 5, 7-11, and 18 depend directly or indirectly from base claim 1. Accordingly, it follows that they are also not anticipated by Bonyhadi et al.

35 U.S.C. 103(a)

With respect to item (6), the Examiner has rejected claims 1-2, 8-11, 18-19 as being unpatentable over Aruffo et al. in view of Efstathiou as further evidenced by Wohlgemuth et al.

As discussed above in item (5), Applicants submit that the limitation of *separate expression* as provided in claims 1 and 19 is patentably distinguishable from the disclosure of Aruffo et al., who fail to teach or disclose the separate expression of CD8 polypeptide and a therapeutic molecule of interest.

Likewise, Efstathiou et al. do not disclose *separate expression* of CD8 polypeptide and a therapeutic molecule of interest. If the Examiner may note, nowhere within Efstathiou is there any teaching of the use of CD8 polypeptide. Thus, one skilled in the art would not read Efstathiou et al. and find it obvious to modify the teachings of Aruffo et al. to arrive at the invention of the present application. Moreover, if one skilled in the art were to take the teachings of Efstathiou et al. and Aruffo et al. to their natural conclusions, one would have modified a herpes simplex virus to express gp39-CD8 fusion proteins out of the LAT promoter.

Claims 2, 8-11, and 18 depend directly or indirectly from base claim 1. As such, these claims must be read to include the limitations set forth in independent claim 1. Specifically, claims 2, 8-11, and 18 must be read to include the *separate expression* of CD8 polypeptide and a therapeutic molecule of interest.

As noted above, Aruffo et al. and Efstathiou et al. fail to teach or disclose separate expression of a CD8 polypeptide and a therapeutic molecule of interest. Aruffo et al. teach fusions of gp39 that are preferably made by fusing gp39 extracellular domains to CD8 extracellular domains. Efstathiou et al., on the other hand, teach latent protein expression out of the LAT promoter. Because Aruffo et al. and Efstathiou et al. fail to teach seminal aspects of the

present invention, Applicants submit that a person skilled in the art reading Aruffo et al. and Efstathiou et al. would not find it obvious to modify Aruffo et al. in the manner taught by Efstathiou et al. to obtain the inventions set forth in these dependent claims. Accordingly, Applicants submit that claims 2, 8-11, and 18 can not be rendered obvious by Aruffo et al. in view of Efstathiou et al.

It should be noted that the Examiner cited Wohlgemuth et al. solely to show that the CD8 sequence has been disclosed.

With respect to item (7), the Examiner has rejected claims 1-2, 8-11, 18-19 under 35 U.S.C. § 103(a), as being unpatentable over Aruffo et al. in view of Salvetti et al., as further evidenced by Wohlgemuth et al.

Applicants respectfully disagree. As discussed above in item (5), Applicants submit that Aruffo et al. fail to teach or disclose the limitation of separate expression of a CD8 polypeptide and a therapeutic gene of interest. The utility of Aruffo et al. is their teaching that the expression of gp39 protein is preferred as a fusion protein with CD8.

To reiterate, the *separate expression* of a CD8 polypeptide and a therapeutic molecule of interest, as recited by independent claims 1 and 19, is well supported in the present application. Support for *separate* expression of the first and second nucleic acid sequences, which will *a priori* produce *separate* polypeptide chains of CD8 and a therapeutic gene of interest, can be found in paragraphs [014], [041], [106], and [108], of the present application as published.

Specifically, paragraph [014] discloses an expression vector comprising a nucleic acid sequence encoding for the CD8 polypeptide, and can include a nucleic acid sequence encoding a therapeutic transgene in the same vector as the CD8 polypeptide, or in another embodiment, in a separate vector. Paragraph [041] similarly describes an embodiment in which the CD8 molecule and therapeutic transgene are on one vector, and an alternative embodiment in which the CD8 molecule and therapeutic transgene are provided by separate expression vectors.

Paragraph [106], as filed, provides that an expression vector, such as that of the present invention, includes transcriptional and translational regulatory nucleic acid sequences operably linked to a nucleic acid encoding a particular protein. In addition, each transcriptional and

translational regulatory nucleic acid sequence, as provided in paragraph [108], includes transcriptional and translational start and stop sequences.

Since the present application provides that each transcriptional and translational regulatory nucleic acid sequence of the present invention is linked to the nucleic acid encoding of a particular protein, and since each transcriptional and translational regulatory nucleic acid sequence of the present invention includes start and stop sequences, it follows that whether the transcriptional and translational regulatory nucleic acid sequence encoding the protein that expresses the CD8 polypeptide and the transcriptional and translational regulatory nucleic acid sequence encoding the protein that express the therapeutic transgene are on the same vector or separate vectors, the presence of the start and stop sequences for each transcriptional and translational regulatory nucleic acid sequence can only result in the separate expression of the CD8 polypeptide and the therapeutic transgene.

As for Salvetti et al., it is noted that nowhere within Salvetti et al., is there any teaching or disclosure of *separate expression* of CD8 and/or a therapeutic molecule of interest, as set forth in claims 1 and 19. Because both Aruffo et al. and Salvetti et al. fail to teach or disclose CD8 polypeptide *separately expressed* from a therapeutic molecule of interest, it would not be obvious to one skilled in the art to make the modifications suggested by the Examiner to arrive at the claimed invention.

Moreover, even if one skilled in the art were to modify the teachings of Aruffo et al. in view of Salvetti et al., the resulting protocol would yield adeno-associated viral vectors with heterologous inserts that encode for gp39-CD8 fusion proteins, for enhanced expression of gp39, which is a ligand for CD40, a member of the Tumor Necrosis Factor Receptor Superfamily. Accordingly, Applicants submit that a person skilled in the art reading Aruffo et al. and Salvetti et al. would not find it obvious to modify Aruffo et al. in the manner taught by Salvetti et al. to obtain the inventions of independent claims 1 and 19.

Claims 2, 8-11, and 18 depend directly or indirectly from base claim 1. As such, these claims must be read to include the limitations set forth in independent claim 1. Specifically, claims 2, 8-11, and 18 must be read to include the *separate expression* of CD8 polypeptide and a therapeutic molecule of interest.

As noted above, Aruffo et al. and Salvetti et al. fail to teach or disclose separate expression of a CD8 polypeptide and a therapeutic molecule of interest. Rather, Aruffo et al. teach fusions of gp39 that are preferably made by fusing gp39 extracellular domains to CD8 extracellular domains. Salvetti et al., on the other hand, teach adeno-associated viral vectors with heterologous inserts. Because Aruffo et al. and Salvetti et al. fail to teach seminal aspects of the present invention, Applicants submit that a person skilled in the art reading Aruffo et al. and Salvetti et al. would not find it obvious to modify Aruffo et al. in the manner taught by Salvetti et al. to obtain the inventions set forth in these dependent claims. Accordingly, Applicants submit that claims 2, 8, 9, 10, 11, and 18 can not be rendered obvious by Aruffo et al. in view of Salvetti et al.

It should be noted that the Examiner cited Wohlgemuth et al. solely to show that the CD8 sequence has been disclosed.

With respect to item (8), the Examiner has rejected claims 1, 2, 8-11, 18, and 19 under 35 U.S.C. § 103(a), as being unpatentable over Aruffo et al. in view of Baru et al., as further evidenced by Wohlgemuth et al.

As discussed above in detail in items (5) - (7), Aruffo et al. fail to teach or disclose that CD8 polypeptide is *separately expressed* from a therapeutic molecule of interest. Rather Aruffo et al. teach gp39-CD8 fusion proteins. Since a *fusion* protein is made when two different proteins are contiguously expressed as the same polypeptide product of a single *fused* gene, *separate* expression of two polypeptides as the product of two genes is not the same as the expression of a *fusion* gene.

Further, Baru et al. fail to teach or disclose separate expression of a therapeutic gene of interest and a CD8 polypeptide. Rather, Baru et al. teaches liposome delivery systems for that consists of liposomes, influenza virus-derived peptides and plasmids that contain heterologous inserts. Nowhere does Baru et al. teach or disclose CD8 polypeptide *and* a therapeutic gene of interest, *separately expressed*.

Since both Aruffo et al. and Baru et al. fail to teach the *separate expression* of CD8 polypeptide and a therapeutic gene of interest of claims 1 and 19, a person skilled in the art

reading Aruffo et al. in view of Baru et al. would not find it obvious to modify Aruffo et al. in the manner taught by Baru et al to obtain the inventions claimed in claims 1 and 19.

Moreover, even in Baru et al. could be combined with Aruffo et al., the resulting protocol would not be directed to the *separate expression* of CD8 polypeptide and a therapeutic gene of interest. Rather, a protocol for liposome transfection including an influenza virus-derived peptide, and a heterologous insert of either Factor XIII, Factor IX, or a gp39-CD8 *fusion* would be the result.

Claims 2, 8-11, and 18 depend directly or indirectly from base claim 1. As such, these claims must be read to include the limitations set forth in independent claim 1. Specifically, claims 2, 8-11, and 18 must be read to include the *separate expression* of CD8 polypeptide and a therapeutic molecule of interest.

As noted above, Aruffo et al. and Baru et al. fail to teach or disclose separate expression of a CD8 polypeptide and a therapeutic molecule of interest. Rather, Aruffo et al. teach fusions of gp39 that are preferably made by fusing gp39 extracellular domains to CD8 extracellular domains to create gp39-CD8 fusion proteins to enhance the usefulness of a gp39 reagent. Baru et al., on the other hand, teach liposome-derived delivery systems, including an influenza virus-derived peptide and heterologous inserts, specifically of Factor VIII and Factor IX expression vectors. Because Aruffo et al. and Baru et al. fail to teach certain aspects of the present invention, Applicants submit that a person skilled in the art reading Aruffo et al. and Baru et al. would not find it obvious to modify Aruffo et al. in the manner taught by Baru et al. to obtain the inventions set forth in these dependent claims. Accordingly, Applicants submit that claims 2, 8-11, and 18 can not be rendered obvious by Aruffo et al. in view of Baru et al.

It should be noted that the Examiner cited Wohlgemuth et al. solely to show that the CD8 sequence has been disclosed.

With respect to item (10), the Examiner has rejected claims 1, 2, 4, 5, 7-11, and 18-30 under 35 U.S.C. § 103(a), as being unpatentable over Zimmer et al. in view of Bonyhadi et al.

As discussed above in item (9), independent claims 1 and 19 have been amended to recite *separate* transcription control elements, such that CD8 and a therapeutic molecule of interest are

separately expressed. Likewise, independent claim 20 has been amended to recite *separate* transcription control elements. Support for the amendment of claim 20 is the same as the support for the amendments of claims 1 and 19, that is, it can be found in paragraph [108] of the present application as published. In particular, paragraph [108] states, "[i]n general, the transcriptional and translational regulatory sequences may include, but are not limited to, promoter sequences, ribosomal binding sites, transcriptional start and stop sequences, translational start and stop sequences, and enhancer or activator sequences. In a preferred embodiment, the regulatory sequences include a promoter and transcriptional start and stop sequences." Control of transcription, as well understood in the art, includes controlling the start and stop of transcription. Moreover, as provided above, each transcriptional regulatory and translational regulatory sequences of the present invention is linked to the nucleic acid encoding a particular protein, and includes start and stop sequences, as provided in paragraph [106]. Since each nucleic acid sequence has its own transcriptional start and stop sequences, it follows that the transcription control elements are *separate*. It should be noted that when each of the first and second nucleic acid sequences has its own separate transcriptional start and stop sequences, the first and second nucleic acid sequences will be independently transcribed into separate mRNAs as a function of their separate transcription control elements, and ultimately translated into separate polypeptides.

As discussed above in item (9), Bonyhadi et al. fail to teach or disclose *separate* transcription control elements. Rather, Bonyhadi et al. teach a bicistronic message for expressing CD8 and *trans*-dominant mutants of the reverse transcriptase RevM10. As it is known in the art, a bicistronic message allows two different proteins to be translated from the *same* mRNA strand, usually from a promoter and an internal ribosome entry site.

Zimmer et al. also fail to teach or disclose *separate* transcription control elements. Moreover, Zimmer et al. fail to teach or disclose the separate expression of a CD8 α-chain extracellular domain and a therapeutic molecule of interest, based on separate transcription control elements.

Since both Bonyhadi et al. and Zimmer et al. fail to teach certain aspects of claims 1, 19 and 20, as amended, a person skilled in the art reading Zimmer et al. in view of Bonyhadi et al.

would not find it obvious to modify Zimmer et al., in the manner taught by Bonyhadi et al. to obtain the inventions of claims 1, 19, and 20.

Moreover, even if Zimmer et al. can be combined with Bonyhadi et al., the result would not be an isolated polynucleotide or an improved expression vectors that supports the separate expression of CD8 and a therapeutic molecule of interest based on separate mRNA transcripts. Instead, the combination of Zimmer et al. and Bonyhadi et al. would be an adenoviral-based therapy directed against HIV infection based on expression of a *trans*-dominant mutants of RevM10.

Claims 2, 4, 5, 7-11, 18, and 21-30 depend directly or indirectly from base claims 1, 19, and 20. As such, they must be read to include the limitations set forth in independent claims 1, 19, and 20. Specifically, claims 2, 4, 5, 7-11, 18, and 21-30 must be read to include *separate* transcription control elements.

As noted above, Bonyhadi et al. fail to teach or disclose *separate* transcription control elements. Zimmer et al. also fail to teach or *separate* transcription control elements that leads to separate expression of CD8 and a therapeutic molecule of interest. Because Zimmer et al. and Bonyhadi et al. fail to teach seminal aspects of the present invention, Applicants submit that a person skilled in the art would not find it obvious to modify Zimmer et al. in the manner taught by Bonyhadi et al. to obtain the inventions set forth in these dependent claims. Accordingly, Applicants submit that claims 2, 4, 5, 7-11, 18, and 21-30 cannot be rendered obvious by Zimmer et al. in view of Bonyhadi et al.

New Claims 32-42

New claims 32-42 have been added to set forth certain novel features of the present invention. Support for the new claims may be found throughout Applicants' specification and drawings as originally filed. No new matter has been added.

Independent claim 32 is directed to a composition including a target cell contacted by an expression vector encoding an immunomodulatory CD8 polypeptide consisting of all or a functional portion of a CD8 α-chain resulting in expression of the CD8 α-chain on the surface of

the target cell. Support for this claim may be found, for example, in paragraphs [011], [041] and [050] of the present application as published, as well as in Example 3. Support for *immunomodulatory* can be found throughout the specification as originally filed, and in particular in paragraphs [040], [041], and [048], of the present application as published, which disclose the expression of an *immunomodulatory* molecule such as CD8.

Dependent claim 33 is directed to a composition wherein the target cell is a cell found in a tissue or organ. Support for this claim may be found, for example, in paragraph [058] of the present application as published.

Dependent claim 34 is directed to a composition wherein the tissue or the organ is one of a liver, a skin or an intestinal tract. Support for this claim may be found, for example, in paragraph [058] of the present application as published.

Dependent claim 35 is directed to a composition wherein the target cell can be present as a single entity, or can be part of a larger collection of cells. Support for this claim may be found, for example, in paragraph [058] of the present application as published.

Dependent claim 36 is directed to a composition wherein the larger collection of cells is one of a cell culture, a tissue, an organ, or an organ system. Support for this claim may be found, for example, in paragraph [058] of the present application as published.

Dependent claim 37 is directed to a composition wherein the tissue is an epithelial tissue. Support for this claim may be found, for example, in paragraph [058] of the present application as published.

Dependent claim 38 is directed to a composition wherein the organ is one of a heart, a lung or a liver. Support for this claim may be found, for example, in paragraph [058] of the present application as published.

Dependent claim 39 is directed to a composition wherein the organ system is a nervous system. Support for this claim may be found, for example, in paragraph [058] of the present application as published.

Dependent claim 40 is directed to a composition wherein the target cell, transplanted in to the recipient, specifically inhibits an immune response in the host against vector-associated antigens. Support for this claim may be found, for example, in paragraphs [010], [013], [057] and [154] of the present application as published.

Dependent claim 41 is directed to a composition wherein the CD8 α-chain is a human CD8 α-chain. Support for this claim may be found, for example, in paragraph [071] of the present application as published.

Dependent claim 42 is directed to a composition wherein the CD8 α-chain consists of a CD8 α-chain extracellular domain and a transmembrane domain. Support for this claim may be found, for example, in paragraphs [012] and [015] of the present application as published.

CONCLUSION

Based on the changes and remarks provided above, Applicants submit that the pending claims are clear, concise, and are neither anticipated nor rendered obvious by the cited references. Accordingly, Applicants submit that pending claims 1-2, 4-11, 18-23, and 25-42 are in condition for allowance. Withdrawal of the pending rejections, and early and favorable reconsideration are respectfully solicited. In the event that a telephone conversation would further prosecute and/or expedite allowance, the Examiner is invited to contact the undersigned at (617) 310-6000.

Applicants do not believe that any additional fees are required in connection with this Response. However, should any fees be required for timely consideration of the present application, Applicants hereby petition for same and request that the fees required for timely consideration of this application be charged to Deposit Account No. 50-2678, Reference 108674-010401.

Respectfully submitted,

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